Remarks

The Examiner withdrew claims 14-16 from consideration as being directed to a non-elected invention. Applicant has cancelled these claims without prejudice and reserves the right to pursue these claims in a continuation application.

Claim Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claim 1-6 and 9-11 under 35 U.S.C. §103(a) as being unpatentable over the combination of U.S. Pat. No. 4,752,549 to Cooke et al ("Cooke") and Walker (TEM, 5(5): 195-200; "Walker") in view of Maciejewski et al. (J.Biol.Chem. 270(17):27661-27665; "Maciejewski") for the reasons of record in the previous Office Action. The Examiner asserts that Cooke teaches recombinant prolactin, Walker teaches that phosphorylated prolactin has antagonistic activity, and that Maciejewski et al. teach that a mutation of serine to glutamic acid in recombinant prolactin mimics phosphorylation. Applicant is pleased to note that the Examiner has recognized that Maciejewski et al. "do not teach that substituted prolactin acts as a prolactin receptor antagonist."

The Examiner states that "Walker teaches that phosphorylation results in antagonism." However, Walker fails to teach that modified recombinant non-phosphorylated prolactin acts to antagonize the growth-promoting effects of non-phosphorylated prolactin. Applicant respectfully submits that Maciejewski fails to overcome this deficiency. Maciejewski does not teach that modified prolactin, in which the serine at position 90 has been replaced with glutamic acid, acts to antagonize the growth-promoting effects of non-phosphorylated prolactin as claimed in the present application. As discussed in more detail below, Maciejewski merely teaches that the mutation of serine to glutamic acid at position 90 in recombinant prolactin produces a protein that, like phosphorylated prolactin, is not mitogenic in the Nb2 cell proliferation assay. Maciejewski fails to teach that the S90E mutation mimics phosphorylation to the extent that modified, recombinant prolactin could act as an antagonist. Thus, one of ordinary skill in the art would not have been motivated to combine these references and Applicant submits that this rejection should be withdrawn.

Applicant recognizes that Maciejewski is cited by the Examiner for the teaching that "substitution of serine with glutamic or aspartic acid mimics phosphorylation." However, this

statement must be read in the context of the entire paper, and, in particular, the underlying experimental data. Applicant respectfully submits that Maciejewski cannot be read to teach that the S90E mutation in recombinant prolactin "mimics all aspects of native phosphorylation" because Maciejewski fails to show that the mutated prolactin has the same activity as phosphorylated prolactin. Maciejewski showed that prolactin with a serine to glutamic acid mutation at position 90 failed to show biological activity in the Nb2 bioassay. They concluded "the similar reductions of ED_{50} values of S90E and phosphorylated bPRLs suggested that glutamic acid was fully capable of functionally replacing phosphoserine" (page 27664, column 1, first full paragraph). However, Maciejewski failed to show any functional data. Rather, their data showed a lack of function. Thus, the conclusion that S90E is a functional replacement for phosphoserine is unfounded and one of skill in the art would not conclude that S90E confers the same properties on recombinant prolactin that phosphorylation confers on native prolactin without further extensive experimentation.

Maciejewski reached their conclusion that the S90E mutation acts like phosphorylation of native prolactin based on a negative result. As the Examiner will surely recognize, a lack of function is not a strong basis for reaching any conclusion, especially in the area of site-directed mutagenesis. It was well known at the time that Maciejewski et al. did their work that many single amino acid mutations produce prolactin that shows greatly reduced activity in the Nb2 assay. For example, Luck et al. (Endocrinology 5:188--1886 (1991)) demonstrated that substitution of either R21 or R177 with a number of other amino acids led to a significant reduction in biological activity in the Nb2 assay. Although Luck's experimental observations are very similar to Maciejewski's, these mutations could not be argued to mimic phosphorylation. Thus, it is not possible to conclude, as Maciejewski does, that a decrease in biological activity in the Nb2 assay is due to functional mimicry of phosphorylation of prolactin.

Maciejewski et al. do not provide any data demonstrating that S90E prolactin acts like phosphorylated prolactin. For example, they fail to demonstrate that replacement of serine at position 90 with glutamic acid produces a protein that can antagonize the growth-promoting effects of non-phosphorylated prolactin. Because Maciejewski does not show that S90E prolactin has activity similar to phosphorylated prolactin, there would be no likelihood of success

in attempting to use mutagenesis to produce a recombinant protein that has the antagonistic activity of phosphorylated prolactin.

In addition, Maciejewski et al. actually teach that the S90E mutation does not mimic all aspects of phosphorylation of prolactin. They found that the mutations S26E and S34E produced a blue shift in their respective U.V. absorbance spectra consistent with that seen for phosphorylated prolactin (page 27664, column 2, last full paragraph). By contrast, "the U.V. absorbance spectra of wild type and S90E bPRLs are nearly identical..." (page 27663, column 1, third full paragraph). Thus, one of skill in the art would conclude that the mutant prolactin does not have all of the properties of phosphorylated prolactin. Because Maciejewski et al. teach that the S90E mutation does not mimic all aspects of phosphorylation of prolactin, it would further be understood by one of skill in the art that their conclusion that S90E mimics phosphorylation is limited to the specific property of reduced mitogenic activity in the Nb2 assay.

Applicant submits that Maciejewski's use of the term "mimics phosphorylation" does not render obvious the present finding that recombinant, mutated prolactin is capable of antagonizing the growth promoting effects of non-phosphorylated prolactin. Maciejewski does not discuss the antagonistic activity of mutated prolactin. Without discussing this activity, it is not possible for the reference to teach that the S90E mutation mimics all aspects of phosphorylation of prolactin. At most, Maciejewski teaches that the S90E mutation in recombinant prolactin mimics phosphorylation of native prolactin to the extent that the recombinant prolactin fails to stimulate cell division in the Nb2 assay. One of ordinary skill in the art would not consider it obvious based on the teachings of Maciejewski that the S90E mutation mimics phosphorylation to the extent that mutated prolactin has antagonistic activity. While the use of the term "mimics phosphorylation" could be construed by one of skill in the art as an invitation to experiment to see if the mutated prolactin has antagonistic activity, in view of the teachings of Maciejewski there would be no expectation of success. Thus, the combination of Walker and Maciejewski does not render the present invention obvious and this rejection should be withdrawn.

Further, Maciejewski teaches away from Walker. The Examiner states that Maciejewski is "essentially silent to the biological activity of antagonism and does not appear to teach away, contrary to Applicant's assertion." However, while Maciejewski may not specifically mention

antagonism, they nevertheless teach away from both Walker and the present invention by stating that "Phosphorylated bPRL does not compete with ^{125}I-labeled nonphosphorylated bPRL for binding to the intermediate form of the PRL receptor found in Nb2 cells" (page 27661, column 2, second full paragraph). Maciejewski go on to propose that phosphorylation produces a conformational change that disrupts the receptor binding site and prevents binding. An inability to compete for binding to the prolactin receptor would indicate to one of skill in the art that phosphorylated prolactin could not act as an antagonist to non-phosphorylated prolactin. The Examiner states that Maciejewski et al. was not cited for its teaching of whether the compound was an antagonist, but rather for the teaching that substitution of serine with glutamic or aspartic acid mimic phosphorylation." Nevertheless, the cited reference contains this contrary teaching and it cannot be ignored.

The Examiner states that "Walker teaches that binding to the receptor is not required for antagonism, contrary to Applicant's assertions." This is simply not true and appears to be based on a misunderstanding of the passage quoted from Walker stating "phosphorylated PRL clearly acts as a superantagonist, with approximately one-tenth the concentration of phosphorylated PRL neutralizing the growth-promoting effect of the rest of the PRL" and "[w]hether this superantagonism is achieved by a much increased affinity for the receptor or initiation of a different signal cascade within the cell is unknown at present." Nothing in this passage indicates that binding to the receptor is not required for antagonism. Rather, the passage indicates that antagonism may be achieved by binding to the receptor especially tightly or by activating a different signal cascade upon binding to the receptor. Thus, Walker does not teach that antagonism could be achieved other than by binding to the receptor and the statements by Maciejewski indicating that phosphorylated prolactin undergoes a conformational change that prevents receptor binding teach away from phosphorylated prolactin acting as an antagonist.

Because Maciejewski et al. do not teach that the S90E mutation is capable mimicking all aspects of native phosphorylation of prolactin, and even teach that it is not, one of skill in the art would not know if S90E prolactin is capable of antagonizing the growth-promoting activity of non-phosphorylated prolactin without extensive experimentation. In addition, Maciejewski teaches away from Walker. As a result, the combination of Walker and Maciejewski does not render the present invention obvious, and this rejection should be withdrawn.

Conclusion

For the reasons presented above, Applicant respectfully submits that all pending claims are in condition for allowance, and an early action to that effect is respectfully solicited. If any issues remain or require further clarification, the Examiner is respectfully requested to call Applicant's counsel at the number listed below in order to resolve such issues promptly.

Respectfully submitted,

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